Understanding chromosome disorders

Unique

SYNGAP1 syndrome

rarechromo.org

What is the SYNGAP1 gene?

Changes (deletions or mutations) affecting the SYNGAP1 gene are a rare cause of developmental delay and intellectual disability (ID). The first description of this gene being associated with problems in humans was in 2009. Since then, several cases have been recognised. It can affect males or females.

The main features of changes in the *SYNGAP1* gene are:

- Need for a variable degree of learning support (intellectual disability is sometimes moderate, but can be more severe)
- Two children in three have seizures
- Need for early support with behaviour that can be challenging
- Low muscle tone
- Constipation
- Sleep problems

Why did this happen?

The gene change in affected children usually occurs as a one-off, random new event around the time of conception (when a baby is made). There is no evidence that this is caused by anything the parents did (or did not do) at the time or during the pregnancy.

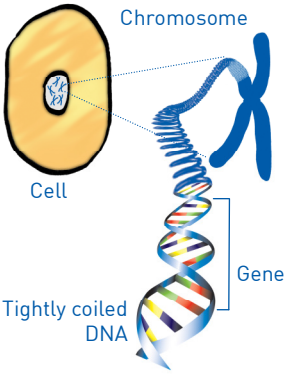
It is theoretically possible that either the mother or father could somehow carry this gene change in just some of their eggs or sperm, which is known as gonadal mosaicism. This risk is likely to be very small (less than 1%), and it is not practical to test for it.

There is one family described in the medical literature where the child has inherited the gene change from their father, who has milder problems, due to the change being present in just some of his cells. This is known as somatic mosaicism.

Children with changes in the SYNGAP1 gene are unlikely to plan to have families of their own. However, should this arise, they would have a 1 in 2 (50%) chance of passing the condition on to their children.

" As a parent it has been immensely helpful to finally receive a diagnosis for our daughter. Without the diagnosis we were always left with lots of unanswered questions. The diagnosis has made us feel that we are not alone and that there are many children who share the same characteristics, problems and hopefully potential solutions."

What causes SYNGAP1 gene changes?



Chromosomes are the structures that contain all our genetic information, in the form of tightly-coiled strings of DNA. Functional segments of DNA, or genes, each give the instructions for a specific component necessary in the form and/or function of our bodies. Most of us have 46 chromosomes, in 23 pairs, in each of the cells in our body. One of each chromosome pair is inherited from our mother and one from our father.

The SYNGAP1 gene is located on chromosome number 6, more specifically in the 6p21.3 region. Similar problems seem to arise whether the gene is altered (mutated) or missing (deleted). This genetic mechanism is called haploinsufficiency.

We know this because affected people with microdeletions of the 6p21.3 region, who have a missing copy of SYNGAP1 and sometimes other genes as well, usually have similar problems to affected individuals with changes within the SYNGAP1 gene alone.

The role of SYNGAP1 is to give the instructions for the production of a protein called SynGAP, which generally suppresses the level of brain activity. When there is not enough SYNGAP1, the brain is generally more excitable. This explains why individuals with changes in the SYNGAP1 gene have the problems they do, especially in the areas of learning, seizures, hyperactivity and sleep disturbance.

" Without a diagnosis you feel lost, though once we received the SYNGAP1 diagnosis we still felt somewhat lost. There was very little literature on the deletion and what we could find was not promising. It was very nice though to have a name to put to it. Having a diagnosis enabled me to connect with Unique as well as to search for new research as it came available. Having a keyword to search on the internet eventually put me in touch with another family in the USA with a little boy just a little older than my daughter Autumn. You would have thought I hit the lottery! After speaking with the little boy's mother, I learned that he might as well have been Autumn's twin – there were so many common issues. We created a group on Facebook for families to connect, and now have a great network of families where we can compare notes, struggles, and triumphs."

Development

" I have seen Autumn do things that we weren't sure would ever be possible. We were never sure that she would walk independently, yet right around her third birthday she accomplished this. We were not sure we would ever hear her voice, and although she is still non verbal she does say 'bike' with regularity. Hearing the voice of your non verbal child is the sweetest thing to ever dance across your eardrums, no matter how fleeting." - age 6

Developmental milestones are generally delayed, typically first walking independently in the third year of life, but this can vary. The child's gait/ style of walking can often remain wide-based, stepping and unsteady. Language acquisition varies: it is usually delayed, but most children use a limited vocabulary of single words, although some can use more than one word together.

Growth

Most babies will have a normal birth weight. Growth measurements are usually within the normal ranges. Some children may have a relatively small head (microcephaly), but again most have head sizes within the normal range.

Feeding

Families should be offered help with feeding as difficulties may be present from the outset, though these usually settle as babies. Children can be slow to wean and are often picky with their food, only eating certain things, and often struggling to use cutlery. Toilet training is often a significant issue.

" Despite Saskia's diagnosis she has a very active life, and loves dancing, singing, dressing up and performance. She will act out a scene as if she was living in it. If Saskia is watching Shrek and is dressed up as Princess Fiona, then she literally transforms into Princess Fiona. Over a 3 year period Saskia has learnt to swim independently without floating aids, and can now jump in the deep end of the pool and swim. What an achievement! Saskia also enjoys horse riding as part of a small Riding for the Disabled Association group, and is doing really well learning to ride an adapted tricycle." - age 10

" For all of her delays Autumn is a smart little girl who knows how to manipulate situations to get what she desires. She is a toddler at heart, and while her body progresses much faster than her mind, we are often reminded to approach the world much more slowly, and to look at things differently, as she would see them. Autumn functions at varying degrees between a 1 and 2½ year old child in a 6 year old's body. Physically she is mostly capable, and although she cannot yet run she is quite a power walker - so we focus on her areas of greatest need. She needs a lot of repetition to really learn something. What might take typical kids 10 tries will take her 100: consistency and constancy are important. Her receptive language (understanding) is more advanced than her expressive language (talking) and she clings to key words and phrases that she understands. If you happen to say 'shoes', she will get her shoes, and want you to put them on with the expectation that you are now going out. We have to be selective in our wording so as to not create a situation that will cause her to melt down." - age 6

" As parents we have ignored those who have advised us that there is a limit to what our child can achieve in relation to speech, language and communication. After investing so much time and effort over the last 7 years in this, it has been so rewarding to finally hear our daughter request things, answer short questions and form short sentences. We were right not to give up." - age 10

Health & wellbeing

Most children with this condition seem to be generally healthy, although some report being particularly prone to common childhood infections when younger. So far, we do not know many adults with changes in the SYNGAP1 gene, but there is no medical evidence to suggest that it should be associated with a shortened lifespan.

Seizures

Around two-thirds of affected children have been formally diagnosed with seizures. These are usually generalised, myoclonic (shock-like jerks), drop attacks (the child goes suddenly limp and may fall) or absences (brief loss of consciousness). Others may report periods of absence, even if not formally diagnosed with seizures. The brain usually appears normal on MRI scanning and these seizures can be difficult to treat.

" Many children with SYNGAP1 have some type of seizure. Absence seizures are easy to miss in children like ours, and after a while you notice patterns to their behaviour that seem questionable. My advice is: don't sit there and guess whether or not there may be a problem, but have your child checked out."

Low muscle tone

Low muscle tone, or hypotonia, is common with children often requiring ankle splints or special boots to aid with walking initially. Walking is often delayed and tends to remain clumsy, with a wide-based and/or high -stepping gait being common.

Joints and spine

Congenital dislocation of the hip is relatively common and some children may develop a curvature of the spine, so careful monitoring and treatment are needed. These problems may be related to severe hypotonia.

Eyesight & hearing

Eyesight and hearing are usually unaffected. However, some people with this condition may have a strabismus (squint). Others may be particularly sensitive to high-pitched or loud noises (hyperacusis).

Other physical problems

Constipation can be a problem, often requiring regular laxatives. Some people have a relatively large amount of fine hair (hirsutism), especially on their legs and arms and down their backs. Some appear to have a subtle, but similar facial appearance, with a broad nasal bridge, a relatively long nose and most consistently a full lower lip. This can be associated with an open-mouthed appearance.

Behaviour

Children can be said to be very loving, but early behavioural support is important, as problems are common – although not universal - and can be significant. Children can struggle with change and often prefer routine. Difficulties can include biting, scratching and/or hair pulling. Children can be hyperactive and have a disturbed sleep pattern. They are often described as 'sensory' and can hand flap when excited. They are sometimes labelled as having autism, although this does not seem to adequately describe all their problems.

" Autumn is an affectionate little girl on her terms. Although she can't say 'I love you', when she wraps her little body around yours and clings to you almost like a koala, you feel that she loves you and needs you with every ounce of her. Along with her strong will comes a temper when she doesn't get her way. Think terrible 2's. A lot of the behaviours she exhibits are in line with what you would expect of a one or two year old. She is self-injurious and if you're not careful you might be bitten as well. I'd like to say this gets better with age, but it really hasn't. She can't communicate verbally that she's angry, but she shows you through her actions.

" Autumn has introduced us to the most infectious belly laugh we have ever heard. She loves watching children play and laughs heartily as they do. The timing of her laughter has always been impeccable and she has taught us to laugh often." - age 6

Support and Information

Rare Chromosome Disorder Support Group,
G1, The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom
Tel/Fax: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

Bridge the Gap SYNGAP Education & Research Foundation
admin@bridgesyngap.org | www.bridgesyngap.org | www.facebook.com/bridgesyngap | www.facebook.com/Syngap1 - 6p21.3

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.
This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The text was written by Dr Michael Parker, Consultant Clinical Geneticist, Sheffield Clinical Genetics Service, UK, and the guide was compiled by Unique.
2015 Version 1.1 (PM)

Rare Chromosome Disorder Support Group Charity Number 1110661
Registered in England and Wales Company Number 5460413